REMARKS

Reconsideration of this application is requested.

It is noted, with appreciation, that the prior art rejections over Anson et al, Fujikawa et al, Anderson et al and Schwinn et al and the formal rejection have been withdrawn.

Claims 17 and 18 have been rejected under 35 USC 102(b) as anticipated by or, in the alternative, under 35 USC 103 as obvious over Osterud et al (hereinafter Osterud) or Suomela et al (hereinafter Suomela). Claims 17 through 20 have been rejected under 35 USC 103 as being unpatentable over Suomela or Osterud, when taken in view of Schwinn et al (hereinafter Schwinn).

At the outset, the applicants wish to express their appreciation of the analysis contained in the official action. It is clear that the Examiner has given this case detailed consideration in light of the response filed December 22, 1988. The outstanding prior art rejections are traversed for the following reasons.

Amendments have been requested in order to clarify the claims and simplify the issues presented for a possible appeal, in two respects.

One amendment cancels a limitation (the polymorphism limitation). This is not now required.

The other amendment recognizes that it is significant that the recombinant DNA-derived factor IX be free of all plasma constituents, i.e. both high molecular proteins and those of

lower molecular weight. It is common knowledge that blood plasma obtained from blood donor services is not hightly purified. This is why subsequent processing of the plasma is required to remove HIV. Despite such processing, the danger of hepatitis viruses and other potentially harmful contaminants remains, thereby giving rise to an urgent public need for pure blood clotting factors. Thus, the provision of a recombinant DNA-derived factor IX protein which is "free from contamination by poxviruses and by all plasma constituents", as required by amended claim 17, not only serves to clearly patentably distinguish the present invention from the cited teachings, but also is highly significant from a practical standpoint.

Referring to the outstanding anticipation and obviousness rejections of claims 17 and 18 over Osterud or Suomela, the Examiner has taken the position that Osterud teaches purification of factor IX to a degree that indicates that it is in fact a homogeneous protein free of high molecular weight contaminants. The Examiner has drawn attention, in particular, to Figure 2 appearing on page 5949 of Osterud which the Examiner contends shows a single band on SDS-PAGE. The Examiner interprets this an indicating that there are no contaminating proteins in that preparation, and that the isolated factor IX was fully active, as indicated at the top left of page 5949.

As regards Suomela, the Examiner has similarly taken the position that homogeneous human factor IX was produced. In regard to both Osterud and Suomela, the Examiner contends that

nothing in those disclosures would lead one to believe that the factor IX preparations are contaminated by high molecular weight impurities.

In response to the Examiner's contention, attention is directed to the attached executed declaration by Professor Brownlee, one of the coapplicants of the present application. In that declaration, Professor Brownlee points out that it is necessary to look at the original prints of Suomela and Osterud, rather than photocopies. When one does so, a very different aspect is cast on the cited teachings. In summary, Professor Brownlee concludes that while Suomela and Osterud claim apparent homogeneity, they do not show clear evidence of that if the papers are examined critically. Inspection of the original prints of the papers shows the presence of high molecular weight contaminants as well as of lower molecular weight. Professor Brownlee points out that Suomela indicates that he has purified his material to apparent homogeneity (see page 152 of Suomela). However, as noted by Professor Brownlee, this is the usual statement made by a cautious scientist implying that there may still be traces of contamination observed or indeed unobserved because of the lack of sensitivity in the procedures.

In order to yet further distinguish the claimed invention from Suomela and Osterud, claims 17 and 19 have been amended, as indicated above, to specify that the factor IX protein is free from contamination by poxviruses and by all plasma

constituents (i.e. both high molecular and low molecular weight contaminants).

Paragraph 3 appearing on page 2 of Professor Brownlee's declaration comments on the Examiner's position beginning in the second paragraph on page 6 of the action. In essence, Professor Brownlee notes that a misunderstanding appears to have occurred concerning high molecular weight contamination of Suomela's product. At the outset, Professor Brownlee clarifies that page 5 of the response of December 22, 1988, in the discussion of Suomela, should have indicated that the gel 4 in Figure 3 on page 150 is not completely free of high molecular weight material towards the top of the gel. Those high molecular weight contaminants appear above the band for factor IX and so cannot possibly be degradation products of lower molecular weight than factor IX. Thus, the suggestions appearing on page 6 of the official action do not explain away the high molecular weight contaminants which are clearly shown in Suomela's Figures 2 and 3.

Paragraph 4 on page 3 of Professor Brownlee's declaration discusses Osterud. Professor Brownlee believes that Osterud clearly shows high molecular weight and low molecular weight contaminants in Figure 1. Professor Brownlee notes that Osterud claims only "greater than 95% homogeneity", which clearly does not equate to the present claimed requirement of being free of all plasma constituents.

In paragraphs 5 and 6 of his declaration, Professor Brownlee takes this homogeneity point one step further by illustrating that it is theoretically virtually impossible to remove all contaminating protein molecules. Even with improved detection methods, many preparations of protein previously taught to be pure clearly show evidence of contamination.

In light of the above, it is believed that both Suomela and Osterud cannot be anticipation references. Professor Brownlee's evidence demonstrates very clearly that both the Suomela and Osterud plasma products are contaminated by high molecular weight and low molecular weight proteins. Impurity bands are clearly visible above the factor IX molecular weight bands when one looks at the original prints. They are even visible where marked on the photocopies attached to the present response.

In light of the above, withdrawal of the outstanding anticipation rejection based on Suomela and Osterud is believed to be in order. Such action is requested.

In regard to obviousness, it is believed that the presently claimed invention would not be obvious to a person of ordinary skill because such a person would not, in practice, carry out such a time consuming purification for the preparation of factor IX from plasma. It is also not obvious that one would wish to carry out any further purification, or that such further purification would remove the high molecular weight contamination. Indeed, Professor Brownlee's comments are believed to be highly relevant in this regard in that, in his

opinion, no protein chemist (he being one) would believe it practicable to attempt to remove all contaminating protein molecules from a protein.

In light of the above, withdrawal of the outstanding obviousness rejections is believed to be in order. Such action is requested.

The remainder of Professor Brownlee's declaration is concerned with the polymorphism point. The Examiner has taken the position that this argument does not point to an actual distinction of a factor IX produced from pooled human plasma as opposed to recombinant factor IX, but rather implies that there is possibility that the recombinant factor IX would differ in part from the factor IX derived from pooled human plasma.

It is clear from Professor Brownlee's declaration that the polymorphism of factor IX is an actual difference, at least in caucasians. However, in view of the amendment to the claims to specify the freedom from all plasma constituents, it is believed unnecessary to pursue the polymorphism argument beyond that which is established by Professor Brownless in his declaration.

A recent case of which the Examiner is presumably aware is Ex parte Gray, 10 USPQ 2d 1922 (B.Pat.App. 1989). That case involved an application relating to human nerve growth factor, identified by a particular amino acid sequence and being free from other proteins of human origin. The human nerve factor was synthesized through the use of recombinant DNA technology and,

thus, was free from human proteins that would otherwise be expected to contaminate the composition. The Examiner rejected the claims as obvious in view of two references which each disclosed human nerve growth factor. In affirming the Examiner's position, the Board noted that the Patent Office did not have the facilities for examining and comparing the appellant's growth factor with that disclosed by the two references, and that the appellants should have shouldered their burden of persuasion with comparisons between their material and cited material to establish unexpected properties for the claimed factor. This the appellants failed to do.

The present invention is distinguished from the Gray case in that, in the present case, their is evidence of record which establishes contamination of the natural product by high molecular weight and low molecular weight proteins even after very intensive purification. There was no such clear distinction in the facts of the Gray case.

Before the present invention, it was not thought that there was any practical means of obtaining the product free of higher and lower molecular weight contaminants while still retaining full activity. In this regard, the claimed product of the present invention is surprising and unexpected over what was thought to be the case prior to the present invention. Both Suomela and Osterud are remote from the claimed invention of the present application in that they produce a product which is not free of all contaminants. Applicants have clearly

proved by way of the declaration evidence in the present case that Suomela and Osterud teach contaminated materials, and therefore do not anticipate or render obvious the presently claimed protein and method.

In light of the above, it is believed that the invention as now claimed in the present application is clearly patentably distinguished over the cited teachings. Withdrawal of the outstanding prior art rejections is therefore respectfully requested.

In the circumstances, it is believed that this application is now in a form suitable for immediate allowance, and early action to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Leonard C. Mitchard
Reg. No. 29,009

LCM:mss
2200 Clarendon Boulevard
14th Floor
Arlington, Virginia 22201
703/875-0400
Attachments: executed declaration and reference